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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,823	10/23/2001	Francesco G. Salituro	VPI/99-01 CON US	1783

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MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/035,823	SALITURO ET AL.
	Examiner Thomas McKenzie Ph.D.	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 14 April 2003.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed-in-accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-13 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>4</u> . | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

1. This action is in response to an election filed on 4/14/03. There are thirteen claims pending and under consideration. Claims 1-3 are compound claims. Claim 4 is a composition claim. Claims 5-13 are use claims. The application concerns some 3-oximino indole compounds, compositions, and uses thereof.

Election/Restrictions

2. Applicant's election without traverse of Group 1 in Paper No. 6 is acknowledged.

3. Objection is made to claims 1, 2, and 4-13 as containing non-elected subject matter. The claimed compounds, compositions, and methods that employ them present a variable core. Formula I contains compounds drawn to the non-elected inventions to the extent it reads upon compounds with $A^1-A^4 = \text{nitrogen}$ or $W = \text{carbon}$.

Title

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: adding the phrase "3-Oximino Indole" to the beginning of the title.

Abstract

5. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and

should include that which is new in the art to which the invention pertains. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, e.g., "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." The abstract is too short and generic. Examiner suggests claim 1, including the figure, and the utility.

Oath/Declaration

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to Applicant Wilke's address. See 37 CFR 1.52(c).

Claim Objections

7. Objection is made to claim 3 under 37 CFR 1.141(a), as containing an unreasonable number of species. To quote the relevant paragraph:

"Two or more independent and distinct inventions may not be claimed in one national application, except that more than one species of an invention, not to exceed a reasonable number, may be specifically claimed in different claims in one national application, provided the application also includes an allowable claim generic to all the claimed

species and all the claims to species in excess of one are written in dependent form (1.75) or otherwise include all the limitations of the generic claim".

Claim 32 contains 356 individually listed compounds. This clearly does not meet the standard of "a reasonable number".

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, and 4-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Line 21, page 127 of claim 1 would appear superfluous after restriction.

9. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. According to MPEP §2173.05(s) "Reference to Figures or Tables Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than

duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted)." The Examiner suggests incorporation of the desired chemicals formulas into the claims, being mindful of the objection concerning number of claimed species made above.

10. Claims 5-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5-13 provides for the use of the composition of claim 4, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 5-13 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Parkinson's disease, does not reasonably provide enablement for preventing any diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the 3-oximino indole compounds such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the

predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before Parkinson's disease occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The paragraphs spanning pages 2-4 and 108 to 110 lists the diseases Applicant intend to treat. Formulations are given in the passage spanning line 9, page 112 to line 29, page 115. The dosage to be used is found in the passage spanning line 30, page 112 to line 12, page 113. A 10,000-fold range of doses proposed. Since no compound with Applicants mechanism of action has ever been used to treat any disease, how is the skilled physician to choose the proper dose from the information in the specification? The single *in vitro* assay used to screen Applicants compound is described in the passage spanning line 17, page 125 to line 5, page 126 but it is unclear how this assay is correlated to prevention of any human disease.

3) There are no working examples of any claimed compound in any formulated form~~s~~ required for medical use. There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical medicine and are therefore physiological in nature.

5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become afflicted with Parkinson's disease before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in neurology diseases with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of Parkinson's diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent Parkinson's disease generally. That is, the skill is so low that no compound effective generally against the multitude of claimed disorders has ever been found let alone one that can prevent such conditions.

7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients,

not just those undergoing therapy. The claims read on the prevention of dozens of unrelated diseases and on the multitude of compounds embraced by Formula I. Thus, the breadth of the claims is very large.

The Examiner suggests deletion of the word "prevention".

12. Claims 5-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Parkinson's disease, does not reasonably provide enablement for treating the multitude of diseases embraced by these claims. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. "The factors to be considered in making an enablement rejection have been summarized above. a) Determining if any particular claimed compound would treat any particular claimed disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different claimed diseases described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning treating claimed diseases, formulations, and dosages used is found in the passages cited above. There is a single *in vitro* assay described in the passage spanning line 17, page 125 to line 5, page 126. Applicants do not assert and it is not art recognized that this assay is

correlated to clinical efficacy for treatment of any human disease. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in JNK related diseases is that no drugs working by this mechanism are currently in clinical use. Search of Medline reveals only two clinical reports concerning JNK inhibitors, one for Crohn's disease (Hommes et al, "Inhibition of stress-activated MAP kinases induces clinical improvement in moderate to severe Crohn's disease" Gastroenterology, 2002 Jan; 122(1), pages 7-14) and Bozyczko-Coyne (Curr Drug Target CNS Neurol Disord) which teaches that a clinical trial in Parkinson's is under way for the compound CEP-1347. No other disease are presently understood as treatable by such inhibitors.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the hundreds of thousands of compounds of formula I as well as the hundred of diseases embraced by the claims. Thus, the scope of claims is very broad.

MPEP 2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

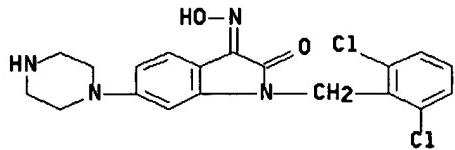
A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

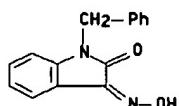
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5, and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Gaeta (WO 99/65875 A1). The compound shown below fits formula (I) with $A_3 = CR^2$, $R^2 = R^5 =$ the non-aromatic heterocyclic ring piperazine, $Y = CH_2-Q_1$, and $Q_1 =$ the substituted phenyl group 2,6-dichlorophenyl. It has Registry Number 252579-10-5 and is found in line 6, page 17 of the reference. It is called Compound XI. Biological activity is taught in line 19, page 25. See also claim 30. Compositions are taught in claim 29. Thus, Applicants claim 4 is anticipated.

Claims 1, 2, 15, 16, and 22-28 of the reference teach cancer treatment with the above compounds. Thus, Applicants' claim 5 is anticipated. The testing protocol described in lines 6-11, page 27 uses the phrase "tumor masses". Thus, Gaeta (WO 99/65875 A1) possessed the concept of treating solid tumors with the compounds above and Applicants claim 13 is anticipated.

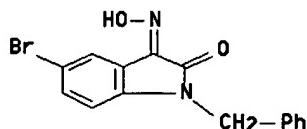


14. Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Esaki (EP 685,463 A1, ref B5). The compound shown below fits formula (I) with $A_3 = CR^2$, $R^2 = R^5 = \text{hydrogen}$, $Y = CH_2-Q_1$, and $Q_1 = \text{phenyl}$. It has Registry Number 28150-91-6 and is found in schematically on page 10 of the reference as compound (22). See also the passage spanning line 51, page 28 to line 4, page 29.



15. Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Guerry (WO 96/16046 A1, ref B1). The compound shown below fits formula (I) with $A_3 = CR^2$, $R^2 = R^5 = \text{bromine}$, $Y = CH_2-Q_1$, and $Q_1 = \text{phenyl}$. It has Registry Number

179943-10-3 and is found in the passage spanning line 35, page 78 to line 2, page 79 of the reference.

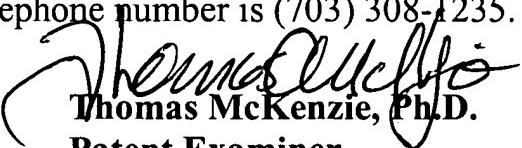


Allowable Subject Matter

16. Claim 3 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

17. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.


Thomas McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK
June 20, 2003

